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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,714	06/04/2007	Jane K. Relton	2159.0450001/EJH/SAC	2306

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STERNE, KESSLER, GOLDSTEIN & FOX, P.L.L.C.
1100 NEW YORK AVE., N.W.
WASHINGTON, DC 20005

EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,714	RELTON ET AL.	
	Examiner	Art Unit	
	SANDRA WEGERT	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6, 10-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/12/06,1/26/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Claims 1-6 and 10-23 are pending. Claims 7-9 have been cancelled. Claim 6 has been amended. The Information Disclosure Statements, sent 12 September 2006 and 26 January 2009, have been entered into the record. Applicant's election of species: SEQ ID NO: 3, Parkinson's disease, HB 7E11 antibody, and SEQ ID NO: 17 as the antigen, without traverse, in the Paper of 6 July 2009, is acknowledged.

Claims 1-6 and 10-23 are under examination in the Instant Application.

Claim Rejections/Objections

Typographic-

Claim 15 is objected to for an obviously typographical error: line 2, "an polypeptide" should be "a polypeptide."

Claim Rejections - 35 USC § 112, first paragraph – Breadth.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-6 and 10-21 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method of promoting regeneration or survival of

dopaminergic neurons in the striatum of mammals injected with 6OHDA (6-hydroxy-dopamine) by administering soluble NgR1 intracranially shortly after injecting 6OHDA, does not enable a method of promoting regeneration or survival of dopaminergic neurons in a mammal in which dopamine neurons died from a degenerative disease, or in which the sNgR1 receptor is not administered intracranially, or in which NgR antagonists other than sNgR1 are administered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The specification does not reasonably provide enablement for an all-encompassing method of promoting regeneration or survival of dopaminergic neurons in a mammal by administering an antagonist of NgR1 other than sNgR1, or by any route of administration other than directly into the brain at the site of injury. The claims however embrace all methods of promoting restoration of dopamine neurons after any injury in the brain involving dopamine neurons, including those involved in human diseases such as Parkinson's disease, and those using any antagonist of NgR besides sNgR1. Dependent claims specifically recite administration into the central nervous system or the striatum. Additional claims recite administration by infusion, administration of SEQ ID NO: 3, use of a fusion protein of NgR1, the species of antibody fused to NgR1, the antigenic fragment used to generate the antibody, and the doses of antagonist used. Experiments presented in the specification show that NOGO receptor (NgR) knockout mice display less apparent cell loss when injected with 6OHDA (a toxin that specifically targets dopaminergic neurons throughout the brain). The inventors used conventional tests of dopaminergic cell number and function, such as tyrosine hydroxylase (TH) staining in the striatum (the enzyme used to produce dopamine), as well as movement studies in which the

6OHDA is injected into one side of the striatum only, and the mouse's rotational bias toward the contralateral side is measured. However, the claims also embrace methods of treating all dopaminergic brain disorders, using any NgR1 antagonist, and by any means of administration. The claims also encompass methods of treating diseases that involve dopamine cell degeneration, including those that are not confirmed as involving the NOGO receptor.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In addition, the instant Application also does not reasonably provide enablement for use of variants of NgR1, such as amino acids 26-310 of SEQ ID NO: 3 *with up to ten conservative amino acid substitutions*. Although amino acids 26-310 of SEQ ID NO: 3, the soluble form of NgR1, appears to act as an antagonist at NOGO receptors in the striatum (Figure 2B), no variants of sNgR1 were made or used in any of the experiments described. In fact, as pointed out above, there are no examples of NgR1 antagonists used for the experiments aside from a peptide consisting of amino acids 26-310 of SEQ ID NO: 3. There are no examples of variant peptides, especially those that inhibit NgR1 other than the one polypeptide provided in the Specification. Similarly, the instant Disclosure does not teach which modifications or mutations in residues 26-310 of SEQ ID NO: 33 are tolerated such that the activity of inhibiting NgR1 is maintained.

Furthermore, since the claims do not require the variants to have activity, the claims embrace inactive variants. The specification does not disclose how to use such inactive variants.

Likewise, the literature is silent as to the differences or changes that are tolerated in NgR's, and by extension sNgR's, while still maintaining the function of binding NOGO ligand (Barton, et al, 2003, 22(13): 3291-3302). Research with similar receptors shows that minimal experimental mutations (1-3 residues) in the coding sequence cause dramatic functional changes or losses of function, such as those caused by single mutations in the coding sequence of the VWF receptor (Huizinga, et al, 2002, Science, 297: 1176-1179, esp. page 1179, column 2). The instant disclosure does not teach how to use all possible variants of the soluble form of SEQ ID NO: 3.

Due to the large quantity of experimentation necessary to enable a method that promotes regeneration or survival of dopaminergic neurons in any mammal with any degenerative disease involving dopamine neurons; by administering any NgR1 antagonist, including those not discovered or tested; the lack of direction/guidance presented in the specification regarding same; the absence of working examples directed to same; the complex nature of the invention; the lack of information in the current literature; and the breadth of the claims which fail to recite conditions enabled by the specification or only sNgR1 of SEQ ID NO: 3, --undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, first paragraph – Lack of Enablement

Claims 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As explained above, the instant specification does not reasonably provide enablement for a method of promoting regeneration or survival of dopaminergic neurons in a subject with Parkinson's disease by administering an antagonist of NgR1. The claims embrace a method of treating Parkinson's disease, which is a disease of dopaminergic cell degeneration, without confirming that preservation or regeneration of nigral striatal cells in Parkinson's disease involves the NOGO receptor. In fact, recent evidence indicates that cells of the substantia nigra do not express the NgR receptor at all (Hunt, et al, *Molecular and Cellular Neuroscience* **20,** 537–552, p. 543, second column), making them poor candidates for regeneration by the claimed method.

Due to the large quantity of experimentation necessary to enable a method that promotes regeneration or survival of dopaminergic neurons in Parkinson's disease; by administering an NgR1 antagonist, including those not discovered or tested; the lack of direction/guidance presented in the specification regarding same; the absence of working examples directed to same; the complex nature of the invention; and the information in the literature that striatal dopaminergic cells lack the NgR receptor; --undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

35 USC § 112, first paragraph – Written Description.

Claims 1-6, 10-17 and 19-23 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of administering an NgR *antagonist* to promote survival of dopaminergic neurons in a mammal. Further claim limitations specify that the soluble NgR receptor (amino acids 26-310 of SEQ ID NO: 3) has up to ten *conservative amino acid substitutions*. Additionally, claims 10-12, 14 and 19-23 recite or embrace use of a *mammalian NgR1*. Claims 15-17 also recite or embrace an antagonist that "binds to *a polypeptide* bound by a monoclonal antibody." Similarly, applicants were not in possession of a genus of antibodies that bind *a polypeptide comprising SEQ ID NO: 3*, as recited in claim 17, for use in the claimed method.

The specification teaches use of the soluble form of NgR, amino acids 26-310 of SEQ ID NO: 3, used as a NOGO receptor antagonist in mice injected with the neuronal toxin 6OHDA. The instant specification also teaches an antibody made against SEQ ID NO: 3. However, the specification does not teach functional or structural characteristics of: 1) all NgR *antagonists* embraced by the claims; 2) variants of the soluble receptor with up to ten *conservative amino acid substitutions;* 3) all *mammalian NgR1* receptors (there are surely several, including those not yet identified); 4) antagonists that bind *a polypeptide bound by* the antibody (which would include compounds that bind outside of the antigenic region); nor of, 5) antibodies that *bind a polypeptide comprising* SEQ ID NO: 3 (which likewise would include those that bind outside of

the antigenic region, or that bind unrelated peptides that also comprise SEQ ID NO: 3). The description of one polypeptide sequence used for the claimed method (amino acids 26-310 of SEQ ID NO: 3) is not adequate written description of an entire genus of functionally-equivalent polypeptide sequences, or unidentified antagonist molecules that may not necessarily even be polypeptides.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation that the antagonist molecule bind the NgR or that it may have up to ten amino acid substitutions. There is not even identification of any particular portion of the polypeptide that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of amino acids 26-310 of SEQ ID NO: 3, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides or small molecules. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making or using. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The very compound *itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483 (BPAI 1993). In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only amino acids 26-310 of SEQ ID NO: 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections: Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22 and 23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 103 and 104 of copending Application No. 2009/0215691 (serial No. 12/335,328). Although the conflicting claims are not identical, they are not patentably distinct from each other because each application claims an almost identical invention with virtually the same scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Instant claims 22 and 23 are directed to methods of using an NgR antagonist to treat a degenerative neuronal disease such as Parkinson's disease. Claims 103 ands 104 of copending Application 12/335,328 are drawn to methods of treating a central nervous system disease in a mammal by administering soluble Nogo receptor-1 polypeptide. Claim 104 specifically recites treatment of Parkinson's disease. Previous claims in the co-pending application recite amino

acids 26-310 of SEQ ID NO: 9, which has 100% sequence homology to SEQ ID NO: 3 in the instant claims. Thus both sets of claims embrace the use of the same identified sequence to treat the neuronal degeneration associated with Parkinson's disease.

Each specification discloses use of amino acids 26-310 of the NOGO-1 receptor as an antagonist to facilitate growth or recovery of damaged neurons in several in vivo assays in rats or mice (although neither specification uses a model of Parkinson's disease).

Since a method of promoting survival of dopaminergic neurons in Parkinson's disease by administering the soluble NgR1 receptor is the same as the method recited in claims 103 and 104 of copending application 12/335,328, and since both use the same polypeptide sequence, it would be obvious to the artisan of ordinary skill to use each method in the same way to treat Parkinson's disease.

Conclusion: Claims 1-6 and 10-23 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

/SLW/
14 September 2009

/Dong Jiang/
Primary Examiner, Art Unit 1646